REMARKS

1. Claim Interpretation; Basis for Claim Amendments

1.1. The Examiner asserts that the phrase "which codes for said molecule" (claim 1) is a "statement of intended use". We disagree, although we appreciate that the coding relationship has "intended use" ramifications. In conventional DNA expression, it is a statement of the structural relationship between a nucleotide sequence (here, that of the template) and an amino acid sequence (here, that of the encoded molecule), established by the Genetic Code.

We recognize that in the case of the present template-encoded molecule complexes, which is not limited to DNA templates and require that the encoded molecule not be a protein, there is no art-recognized established relationship between the codons of the template and the structural units of the encoded molecule. Presumably, this is the reason for the examiner's "intended use" comment, i.e., the "encoding" is in the mind of the creator.

Claim 1 has been amended to recite

(1) each encoded molecule comprises a plurality of structural units (cp. claim 2)(page 6, line 13);

(2) each template comprises a plurality of codons (page 4, lines 22-24);

(3) the encoded molecules of the microarray collectively provide a plurality of chemically distinct structural units (e.g., R, G and D in example 1);

(4) the templates of the microarray collectively provide a plurality of chemically distinct codons(same, and see P15 for choices for the bases of which the codons are composed, and page 28 for sequences used in example 1);

(5) within a given complex, each codon of the template identifies one of the structural units of the encoded molecule to which the template is complexed (page 22, lines 8-10);

(6) each chemically distinct codon identifies one and only one chemically distinct structural unit (see page 4, lines 7-8, "specific chemical entities")[1];

(7) each template thereby identifies the complete encoded molecule to which it is complexed (page 22, lines 8-10).

As a result of these limitations, there are structural relationships between the templates and the encoded molecules. While the template can be immediately decoded only by one with a priori knowledge of the intended relationship, the coding relationships may be deduced after characterization of a sufficient number of complexes. It is thus possible, by studying a microarray, to determine whether it has the required coding relationship and thus whether it infringes the claim. Since some microarrays cannot possibly satisfy these encoding limitations, it follows that they present more than a mere statement of intended use.

By way of example, suppose that the chemically distinct codons found in the templates of a particular array are identified as 1, 2, 3, 4,.... and the chemically distinct structural units of the encoded molecules as A, B, C, D,....

If a complex contained the template 1212, the encoded molecule could be ABAB (1 identifies A, 2 identifies B) or AAAA (1 and 2 both identify A, analogous to DNA:protein degeneracy) but it could not be AAAB (2 identifies both A and B). So a microarray comprising the complex 1212:AAAB would be non-infringing.

Moreover, if a second complex were 1212:BBBB, this would be inconsistent with the first complex being either 1212:ABAB or 1212:AAAA (even though 1212:BBBB by itself could be an allowable

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[1] This limitation allows for degeneracy analogous to that of the Genetic Code. That is TTT only encodes Phe, and TTC only encodes Phe, so the Genetic Code satisfies this limitation of claim 1, but Phe is encoded by both TTT and TTC. Such degeneracy is excluded by claim 29. (Of course, claim 1 is not limited to use of the Genetic Code.)

degeneracy), and a microarray comprising both such complexes would be non-infringing.

1.2. Claim 1 has also been amended to provide that "the encoded molecules are not nucleic acids". The exclusion of "nucleic acid" is intended to exclude both oligonucleotides and polynucleotides, see P4, L3.

The first basis for exclusion of a nucleic acid from the class of encoded molecules is that nucleic acids are already the preferred class of templates, see P4, L2-3, and therefore hybridize to the probe by base complementarity. If the encoded molecule were also a nucleic acid, then there would be a clearly undesirable competition between the probe and the encoded molecule for binding to the template.

The second basis for exclusion is in Fig. 5. Fig. 5 defines preferred connections between the structural units of the encoded molecule. If the encoded molecule were a nucleic acid, the connection would be a phosphodiester band between the nucleosides. However, no phosphodiester bands are specifically shown in Fig. 5. At best, they are embraced by, the "etc." in the definition of Z and Z' for the second-to-last example in Fig. 5.

Third, mRNA-protein fusions are positively disclosed (p1, L16-24) as part of the background art, and hence can be excluded.

Fourth, original claim 5 recited "wherein the chemical entities are reacted without enzymatic interaction", which at least would exclude the encoded molecule being made by nucleic acid ligation.

Finally, we respectfully submit that if both template and encoding molecule could be complementary nucleic acids, it would not be possible to distinguish them and yet the specification clearly contemplates that they are distinguishable.

1.3. Claim 1 has also been amended to require that "at least one encoded molecule is not a protein composed solely of one or more of the 20 genetically encoded amino acids".

As we explain in more detail in section 5 below, we have

written description for both encoded molecules which are proteins and encoded molecules which are not proteins, and hence could limit claims 22 and 24 to the encoded molecules which are not proteins.

The proteins, in turn may be subdivided into two groups, those which are composed solely of one or more of the 20 genetically encoded amino acids (and thus can be encoded by a nucleic acid) and those which are not. The latter could include, for example, the D-isomers of the genetically encoded amino acids, or amino acids which differ more profoundly from the genetically encoded amino acids.

Basis for the instant limitation is at the bottom of page 1, namely, in

> In one aspect of the invention, it is small molecules which are presented and in another aspect it is unnatural polymers that are presented. Notably, the present invention is not limited to the reaction products of the 20 naturally occurring amino acids

The term "unnatural polymers" would, in the eyes of the person skilled in the art, be taken as referring or at least including proteins which included non-naturally occurring amino acids.

Please note that instead of referring to "naturally occurring amino acids", we refer to "genetically encoded amino acids". While there are 20 genetically encoded amino acids, all of which occur in nature, the set of naturally occurring amino acids (even in naturally occurring polymers) is somewhat larger, including, e.g., hydroxyproline, hydroxylysine, desmosine, isodesmosine. In view of the reference to "20" in the specification, we thought the skilled worker would infer that the applicants were in possession of polymers which expanded beyond the 20 genetically encoded amino acids as well as those which expanded beyond the larger set of naturally occurring amino

acids. New claim 38 is similar to the aforementioned claim 1 limitation except that it requires that "at least one encoded molecule is not a protein composed solely of one or more of the naturally occurring amino acids."

1.4. Claim 25 has been added to provide antecedent basis for the "nascent encoded molecule". Further structural limitations on the components of the microarray are imposed by new claims 26-36 and 38. Claim 37 imposes a process-of-making limitation, which can indirectly affect structure.

1.5. Basis for the new claims is as follows:

Claim 25: Page 6, lines 3 to 4 and lines 10 to 16.
Claim 26: Page 4, lines 7 to 8.
Claim 27: As claim 26.
Claim 28: Page 4, lines 22 to 23
Claim 29: Page 4, lines 13-14 (recites that a one base codon would allow for four different chemical entities; clearly this contemplates that the base could be A, C, G or T and that each of these identifies one and only one chemical entity) and lines 17-18 (this extrapolates to codons of two or three bases, which are said to allow for 4^2 and 4^3 different chemical entities, respectively)
Claim 30: Page 4, lines 7 to 20.
Claim 31:see codons disclosed in Example 1 (which are all of the same length), page 4, lines 13 to 18 (codons which are all 1 base, all 2 bases, or all 3 bases)
Claim 32: Page 4, line 24, page 5, line 3.
Claim 33: Page 4, lines 19 to 20.
Claim 34: Fig. 5.
Claim 35: Page 4, line 22, to page 5, line 20.
Claim 36: Page 5, lines 22 to 25.
Claim 37:
a): Page 3, lines 17 to 18; claim 8 of PCT Pamphlet.
b): Page 2, lines 6 to 7.
c): Page 3, lines 17 to 32.

d): Page 4, lines 1 to 2; page 12, lines 25 to 30; claim 8 of PCT Pamphlet.
i): Page 6, lines 3 to 4; page 7, line 10.
ii): Page 9, lines 24 to 25; page 12, lines 21 to 23..
Claim 38: see end of section 1.3 above.

2. Specification

The hyperlink at page 13 has been inactivated, so it is no longer browser-executable. This satisfies the concerns set forth in MPEP 608.01 while preserving the disclosure.

3. Claim Objections

The claims have been amended as suggested by the examiner.

4. Definiteness Issues

The Examiner states in the second two paragraphs on OA page 3:

> The above claims have multiple antecedent basis issues. First, in claim 1, the phrases "said probes" in line 3 and "said molecule" in line 5 lack antecedent basis because the probes are recited as "single-stranded probes" and the molecules are recited as "encoded molecules". In other words, the above structures are recited generically after they are specifically labeled thus causing a lack of clarity.
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> Similar reasoning applies to the phrases "the nascent encoded molecule" recited in claim 3, "the nascent molecule" recited in claim 4, "the nucleic acid probe" and "the probe" recited in claim 7, "the nascent molecule" recited in claim 11, "the information" and "the nascent complex" recited in claim 12, and "the nucleic acid molecule" and "the array" and "the probe" recited in claims 15, 18, and 21.

The rejection is not well taken. For example, having recited "single stranded probes" previously, it is possible to

refer to them simply as "said probes", so longer as there aren't other probes with which they could be confused. Likewise having recited "encoded molecules", one could refer to "said molecules" as long as the "encoded molecules" were the only "molecules" element identified in the claim.

However, we recognize that the terms "nascent encoded molecule" and "nascent complex" are meaningful only in a process context, such as that of claim 2. Basis for "nascent encoded molecule" in a process context is provided by new claim 25, and for "nascent complex" in amended claim 12. Claims 11 and 13 have been cancelled as redundant with 3 and 4, respectively.

5. Written Description

The examiner states that there is a lack of written description for "encoded molecule is not a protein". While this rejection was directed to claims 22 and 24, a limitation similar to that of claim 24 has been incorporated into claim 1.

We previously cited, as basis for this limitation, the passage at page 1, line 26 to page 2, line 3:

> The prior art is restricted to the presenting of proteins on a microarray. According to an object of the present invention it is desired to expand the type of molecules which can be presented on a microarray. In one aspect of the invention, it is small molecules which are presented and in another aspect it is unnatural polymers that are presented. Notably, the present invention is not limited to the reaction products of the 20 naturally occurring amino acids, which allow for a higher diversity of the presented molecule and the possibility of forming robust and stable molecules that can be treated under harsh conditions, such as high temperature, extreme pH and in media containing detergents.

The Examiner says that "while the disclosure does

positively recite presenting molecules other than proteins on the microarray, i.e., expanding from just proteins, the disclosure in no way presents an embodiment which expressly excludes proteins from the microarray".

MPEP 2173.05(i) says that "if alternative elements are positively recited in the specification, they may be explicitly excluded in the claims". Hence, having recited "protein" in the specification -- not merely at P1, L26 and arguably in example 1, but also at P1, L16-24 -- applicants may exclude it. It is clear that display of a protein is not an essential element of the invention.

Applicants have never contended that the invention as disclosed cannot be practiced with encoded molecules which are proteins. However, they clearly contemplate that there are particular advantages to providing microarrays in which the encoded molecules are <u>not</u> proteins. Clearly, applicants contemplated a dichotomy; a first embodiment in which they are proteins, and a second in which they aren't. Among the non-proteins, there are two explicitly disclosed subgenera, which are "small molecules" and "unnatural polymers".

Encoded molecules and their preparation are further discussed on page 6-8. The encoded molecules are assembled by reactions between the reactive groups of chemical entities, or between the reactive group of a chemical entity or a scaffold. The reactive groups in effect serve as precursors for the structure of the connection between chemical entities in the final encoded molecule, see P8, L28-29.

In a protein, the chemical entities are amino acids, the reactive groups are amino and carboxy groups, and these groups are precursors for peptide bond (-NHCO-) connections. It is evident from Fig. 5 (cited at P8, L29-30) that applicants contemplate a much wider range of connections, wherein only the three nucleophilic substitution reactions yielding "amides" can be characterized as forming a protein. (See also P11, L4-17).

Applicants should not be expected to exhaustively list all of the "non-proteins" in order to have possession of "an encoded molecule which is not a protein".

6. Anticipation Issues

6.1. Claims 1-7 and 11-24 stand rejected as anticipated by Polsky-Cynkin (1985). This reference teaches immobilization of cloned Salmonella DNA on plastic and agarose supports.

The Examiner asserts that the "chemical entities" are not recited in the claim as being a required structural component of the invention, i.e., the encoded molecule.

Claim 1 has been amended to present suitable structural limitations.

It could be argued that in Polsky-Cynkin, since the cloned salmonella DNA is double stranded, the double stranded DNA constitutes a "complex", and that each base (or each triplet) in one strand "identifies" the complementary base in the other strand and thus one serves as a "codon" and the other as a "structural unit". However, amended claim 1 requires that the encoded molecules are not nucleic acids.

6.2. Claims 1-6, 11-14, 16, 17, 20, 22 and 24 are rejected as anticipated by Szostak.

Szostak discloses RNA protein fusions in a microchip format. Szostak's protein is excluded by amended claim 1.

7. Obviousness Issues

Claims 7, 15, 18 and 21 stand rejected as obvious over Szostak in view of Felder.

The Examiner concedes that Szostak does not expressly teach hybridization to a solid support through an adapter oligonucleotide, but urges that it would be prima facie obvious to use of an adapter oligonucleotide to attach another nucleic acid to a microarray in view of Felder.

In view of the amendments to claim 1, it is believed that

Szostak is now deficient in more than just failure to teach an adapter oligonucleotide, and hence the rejection is moot.

Respectfully submitted,

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